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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,860	CORVALAN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 22-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,22,24-32,34-43 and 45* is/are rejected.

7)☒ Claim(s) *2,23, 33 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2 and 22-45 are pending.

2. In view of the amendment filed 11/19/04, the following rejections remain.

3. The disclosure stand objected to for failing to comply with the requirement of 37 C.F.R. 1.821(d), SEQ ID NO is required for Figures 23-40, Appropriate correction is required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 22, 24-32, 34-43 and 45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a human monoclonal antibody or antigen binding portion thereof that binds to Platelet Derived Growth Factor D (PDGFD) comprises a heavy chain amino acid sequence comprising SEQ ID NO: 48 and a light chain amino acid sequence comprising SEQ ID NO: 49; The said human monoclonal antibody or antigen binding portion thereof wherein the heavy chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of GYTFTSYDIN, CDR2 consists the amino acid sequence of INPNSGNTDYAQKFQ, and CDR3 consists the amino acid sequence of GFGYSYNYDYYYGMDV; The said human monoclonal antibody or antigen binding portion thereof wherein the light chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of RASQSVSSSYLA, CDR2 consists the amino acid sequence of ATSSRAT, and CDR3 consists the amino acid sequence of QQYGSSPCS, and a labeled human monoclonal antibody or antigen binding portion thereof mentioned above wherein said monoclonal antibody or antigen binding portion thereof is labeled with a detectable marker for detection assay, **does not** reasonably provide enablement for any human monoclonal antibody that binds to any Platelet Derived Growth Factor D wherein the antibody comprises any combination of heavy and light chain as set forth in claim 1, any human monoclonal antibody that binds to any Platelet Derived Growth Factor D "further comprises any sequence encoded by any "human D5-18 family gene", any human monoclonal antibody that binds to any Platelet Derived

Growth Factor D derived from any "human VH1-8 gene", and any "JH6B family gene" as set forth in claims 22, 30, 32, 40 further comprising a detectable label (claims 31, 41 and 45) and a composition comprising said monoclonal antibody or antigen-binding fragment thereof (claims 42, 43, and 45) for any purpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a human monoclonal antibody or antigen binding portion thereof that binds to only human Platelet Derived Growth Factor D (PDGFD) comprises a heavy chain amino acid sequence comprising SEQ ID NO: 48 and a light chain amino acid sequence comprising SEQ ID NO: 49. The said human monoclonal antibody or antigen binding portion thereof of the heavy chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of GYTFTSYDIN, CDR2 consists the amino acid sequence of INPNSGNTDYAQKFQ, and CDR3 consists the amino acid sequence of GFGYSYNYDYYYGMDV. The said human monoclonal antibody or antigen binding portion thereof of the light chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of RASQSVSSSYLA, CDR2 consists the amino acid sequence of ATSSRAT, and CDR3 consists the amino acid sequence of QQYGSSPCS. The specification further discloses a labeled human monoclonal antibody or antigen binding portion thereof that binds to Platelet Derived Growth Factor D (PDGFD) comprises a heavy chain amino acid sequence comprising SEQ ID NO: 48 and a light chain amino acid sequence comprising SEQ ID NO: 49 wherein said monoclonal antibody or antigen binding portion thereof is labeled with a detectable marker. The specification further discloses various hybridoma cell lines producing monoclonal antibodies comprising the specific heavy chain and the specific light chain amino acid sequences such as the ones shown in Figures 3-21.

The specification does not teach how to make any human monoclonal antibody mentioned above that bind to any PDGF-D. The specification merely discloses human PDGF-D as an immunogen for making the human monoclonal antibody. There is insufficient guidance about the structure of other PDGF-D other than human PDGF-D, much less about the binding specificity of the claimed antibody.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. The specification is silent which human antibody would bind to all PDGF-D other than human PDGF-D. There is a lack of working example demonstrating that the claimed antibody binds to mouse or rat PDGF-D.

Further, it is known that heavy and light chain combine to form antibody and it is the variable domains of the heavy and light chains form the antigen binding site. There is insufficient guidance as to the structure of the light chain in the human monoclonal antibody as recited in claim 1 without the amino acid sequence. The claims encompass any number and/or combination of CDR1, CDR2, and CDR3 from immunoglobulin heavy chain (claims 24-26 and 34-36), any number and/or combination of CDR1, CDR2, and CDR3 from immunoglobulin light chain (claims 27-29, and 37-39). There is insufficient guidance as to which combination of heavy and light chain or which combination of CDR1, CDR2, CDR3 from which heavy chain and/or combination of CDR1, CDR2, CDR3 from which light chain that the undisclosed antibody would maintain the same binding specificity as the claimed antibody that binds specifically to human PDGF-D. The term "comprising" is open-ended. It expands the CDR1, CDR2 and CDR3 regions of heavy and light chain (claims 24-29 and 34-39) to include additional amino acid residues at either end. Given the indefinite number of undisclosed amino acids to be added, there is insufficient guidance as to which amino acids to be added and whether the resulting antibody maintains the same binding specificity.

Janeway et al teach that the association of different heavy and light chain variable regions from the binding site (See page 3:21, last paragraph, in particular). However, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody may adversely affect its activity. Without the amino acid sequence of the light chain, it is unpredictable which undisclosed light chain combining with SEQ ID NO:48 will bind specifically to human Platelet Derived Growth Factor D (PDGFD).

With regard to claims 22, 30, 32 and 42, the specification provides insufficient guidance as to which particular VH1-8 family gene, combined with which JH6B family gene and/or D5-18 family gene that encode the claimed antibody without the nucleotide sequence of said family genes. Further, the term "gene" as defined by Merriam-Webster's Online Dictionary, 10th Edition is a segment of DNA that is involved in producing a polypeptide chain; it can include regions preceding and following the coding DNA as well as introns between the exons. The specification provides insufficient guidance as to the introns as well as exons encoding the undisclosed human monoclonal antibody. In addition to the lack of guidance for the genes mentioned above, there is a lack of guidance as to which undisclosed "sequence encoded by which gene of the human D5-18 family gene without the nucleotide sequence (claim 22). Given the indefinite number of human monoclonal antibody, the is insufficient in vivo working example demonstrating that all disclosed antibody is effective for treating any disease. Since the binding specificity of all human monoclonal antibody mentioned above is not enabled, it follows that any composition comprising said antibody is not enabled. It also follows that all undisclosed monoclonal antibody comprises a detectable marker are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/19/04 have been fully considered but are not found persuasive.

Applicants' position is that contrary to the Examiner's contention that there is insufficient guidance about other PDFGD" the present specification quite clearly defines PDFGD. The Examiner's attention is invited to the specification at page 14 line 25 to page 15. The cited references are not relevant to the current invention. The invention does not pertain to B cell epitopes. Furthermore, the claims are not directed to methods of generating antibodies to PDGFD. Claims are directed to human antibodies that bind to PDGFD. The antigen used to generate the human antibodies of the present invention is disclosed in the specification (see Example 1, page 48). Specifically the gene product of 14EK293 cells transfected with PDGFD produces an active fragment "p35" which was used as the immunogen. PDGFD p35 is known in the art (see LaRochelle et al. Nature Cell Biology 3:517 (2001) which is referenced in the specification at page 14, lines 25-26, copy attached as Attachment A). Briefly, the reference describes cloning of PDGFD CDNA into a mammalian expression vector and subsequent transfection into HEK293 cells. When PDGFD is purified from serum-containing conditioned medium, a principal species, p35, is obtained. Sequence analysis of the amino terminus of p35 shows it is the product of proteolytic cleavage after R247 or R249. PDGFD is secreted as a dimer and is proteolytically processed in the presence of sera to p35. Hence Applicants are not relying on a "peptide fragment" in the way that Kuby refers to "fragments" but rather to a biologically produced end product as purified from conditioned culture media after protein synthesis and secretion. The antibodies of the invention are enabled and Kuby offers nothing to even suggest otherwise. Applicants strongly disagree that there is insufficient guidance provided as preferred germline sequences as well as 19 specific combinations specifically binding PDGFD are provided in the specification (see for example Figures 48 and 49). Also CDRS and framework sequences are also described in the specification (see for example Figures 48-57). Furthermore, the Examiner states that the specification provides insufficient guidance as to the introns as well as exons encoding an antibody of the invention. Applicant disagrees as introns do not code for proteins, and the claims specifically pertain to a protein (antibody) encoded by a human VH1-8, JH6B and D5-18 family gene. Therefore details of genomic introns are irrelevant to enablement of the invention. Applicants also disagree with the Examiner's rejection of claims 24-29 and 34-39 for the use of the term "comprising". These claims each pertain to a specific CDR that is comprised by the human antibody. The antibody, in most cases will also have other CDR

regions, framework regions as well as optionally constant domains. Therefore the open-ended language correctly reflects the invention, "the antibody comprises a heavy or light chain CDR region...".

In response, the scope of the claimed invention is directed to human antibodies that bind to any PDGFD. The specification merely discloses human PDGF-D as an immunogen for making the human monoclonal antibody. There is insufficient guidance about the structure of other PDGF-D other than human PDGF-D, much less about the binding specificity of the claimed antibody. With regard to claim 1, it is known that heavy and light chain combine to form antibody and it is the variable domains of the heavy and light chains form the antigen binding site. There is insufficient guidance as to the structure of the light chain without the amino acid sequence in the human monoclonal antibody as recited in claim 1.

The scope of claims 22 encompasses any human monoclonal antibody that binds to any PDGFD and said antibody is encoded or derived from any human VH1-8, any JH6B family gene and/or D5-18 family gene. The specification on page 51 discloses only 13 antibodies to human PDGFD. The specification is silence whether the claimed antibodies binds to PDGFD other than human Platelet Derived Growth Factor D (PDGFD) encoded by the specific combination of human VH1-8 family gene and JH6B family gene. Without the nucleotide sequence of the family genes mentioned above, it is unpredictable which V sequence combine with which J sequence and/or D sequence to provide a human antibody that binds to any PDGFD.

In contrast to applicant's assertion that introns are irrelevant to enablement of the invention, the definition of a "gene" encompasses introns, exons and promoter regions. Without the nucleotide sequences of the human "VH1-8 family gene", "JH6B family gene", and "D5-18 family gene", it is unpredictable which genes will encode the claimed human antibody. One skill in the art cannot make, much less use the claimed invention.

In response to Applicants' argument the antibody, in most cases will also have other CDR regions, framework regions as well as optionally constant domains. Therefore the open-ended language "comprising" in claims 24-29 and 34-39 correctly reflects the invention, it is correct that antibody contains CDR1-3 from heavy and light chains, framework regions as well as optionally constant domains. However, claim 24 as written lacks the CDR2 and CDR3 from heavy chain, and CDR1, CDR2 and CDR3 from the light chain, for example. Claim 25 as written lacks the CDR1 and CDR3 from the heavy chain, and CDR1-3 from the light chain. Claim 26 as written lacks the CDR1-2 from heavy chain and CDR1-3 from the light chain. Claim 27 as

written lacks the CDR1-3 from the heavy chain and CDR2-3 from the light chain. Claim 28 as written lack the CDR1-3 from the heavy chain, and CDR1 and CDR3 from the light chain. Likewise, claim 29 lacks the CDR1-3 from the heavy chain and CDR1-2 from the light chain. The same reasons apply to claims 34-39. There is insufficient guidance as to the undisclosed CDRs mentioned above in said claims without the specified amino acid sequence.

6. Claims 1, 22, 24-32, 34-43 and 45 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) any human monoclonal antibody that binds to any Platelet Derived Growth Factor D (PDGFD) comprising heavy chain amino acid sequence comprising SEQ ID NO: 48 as set forth in claim 1, (2) any human monoclonal antibody or antigen binding portion thereof that specifically binds to any Platelet Derived Growth Factor D (PDGFD) encoded by or derived from any human VH1-8 family gene, and any JH6B family gene, (3) any human monoclonal antibody or antigen binding portion thereof that specifically binds to any Platelet Derived Growth Factor D (PDGFD) encoded by or derived from any human "VH1-8 family gene", and any "JH6B family gene" further comprising any sequence encoded by a human "D5-18 family gene", (4) any human monoclonal antibody mentioned above further comprises a detectable marker and (5) any composition comprising any antibody mentioned above.

The specification discloses only a human monoclonal antibody or antigen binding portion thereof that binds to human Platelet Derived Growth Factor D (PDGFD) comprises a heavy chain amino acid sequence comprising SEQ ID NO: 48 and a light chain amino acid sequence comprising SEQ ID NO: 49. The said human monoclonal antibody or antigen binding portion thereof of the heavy chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of GYTFTSYDIN, CDR2 consists the amino acid sequence of INPNSGNTDYAQKFQ, and CDR3 consists the amino acid sequence of GFGYSYNYDYYYGMDV. The said human monoclonal antibody or antigen binding portion thereof of the light chain comprises CDR1, CDR2 and CDR3 wherein the CDR1 consists the amino acid sequence of RASQSVSSSYLA, CDR2 consists the amino acid sequence of ATSSRAT, and CDR3 consists the amino acid sequence of QQYGSSPCS. The specification

further discloses a labeled human monoclonal antibody or antigen binding portion thereof that binds to Platelet Derived Growth Factor D (PDGFD) comprises a heavy chain amino acid sequence comprising SEQ ID NO: 48 and a light chain amino acid sequence comprising SEQ ID NO: 49 wherein said monoclonal antibody or antigen binding portion thereof is labeled with a detectable marker. The specification further discloses various hybridoma cell lines producing monoclonal antibodies comprising the specific heavy chain and the specific light chain amino acid sequences such as the ones shown in Figures 3-21.

With the exception of the specific human monoclonal antibody that binds to human PDGF-D comprising the specific combination of heavy and light chains as set forth in claim 23, there is insufficient written description about the structure of the light chain in the monoclonal antibody in claim 1 without the amino acid sequence. Further, the specification discloses only human monoclonal antibody or antigen binding portion thereof that specifically binds to human PDGF-D. There is a lack of a written description about the other PDGF-D to which the claimed antibody binds.

With regard to claims 22, 30, 32 and 42, the family genes such as human "VH1-8 family gene", any "JH6B family gene" and/or human "D5-18 family gene" as recited in claims 22, 30, 32, and 42-43 without the nucleotide sequence have no structure, much less function. The specification provides insufficient written description about which particular VH1-8 family gene and JH6B family gene encode the claimed antibody or which undisclosed human monoclonal antibody that binds to all PGDF-D is derived from which particular human V_H1-8 family gene and J_H6B family gene without the nucleotide sequence (claims 22, 32 and 42). Further, the term "gene" as defined by Merriam-Webster's Online Dictionary, 10th Edition is a segment of DNA that is involved in producing a polypeptide chain; it can include regions preceding and following the coding DNA as well as introns between the exons. However, the specification provides insufficient written description about the introns as well as exons in the germ line that encodes the undisclosed human monoclonal antibody, let alone a gene from the human VH1-8 and JH6B gene that encode any human monoclonal antibody or antigen binding portion thereof that specifically binds to all Platelet Derived Factor D (PDGF-D). Since the structure of the claimed antibody mentioned above are not adequately described, it follows that any human monoclonal antibody further comprises a detectable marker are not adequately described. It also follows that any composition comprising any human monoclonal antibody mentioned above are not adequately described.

Finally, the specification discloses only human PDGF-D to which the claimed antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of PDGF-D to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/19/04 have been fully considered but are not found persuasive.

Applicants' position is that the claims pertain to a human monoclonal antibody that binds to Platelet Derived Growth Factor D, not "any" Platelet Derived Growth Factor. The claims further pertain to certain human monoclonal antibodies comprising a specific heavy chain amino acid sequence (claim 1); a specific light chain amino acid sequence (claim 2); are encoded by or derived from specific germline sequences VH1-8 and JH6B (claims 22, 32); and have specific heavy and light chain amino acid sequences (claims 23, 33); have specific heavy chain CDR1 (claims 24, 34), CDR2 (claims 25, 35), CDR3 (claims 26, 36) or light chain CDR1 (claims 27, 37), CDR2 (claims 28, 38), CDR3 (claims 29, 39) or further comprise D region D5-18 (claims 30, 40). The specification absolutely provides specific written description of human monoclonal antibodies that bind to PDGFD. Nineteen specific examples are provided. Also provided is the analysis of the germline sequences utilized in the in the development of those antibodies which clearly defines the preferred germline sequences to use for obtaining antibodies that bind to PDGFD and such are clearly provided in the specification and pending claims. The specification absolutely provides specific written description of human monoclonal antibodies of the sequences defined in the pending claims. Applicants also disagree with the Examiner's rejection of claims 24-29 and 34-39 for the use of the term "comprising". These claims each pertain to a specific CDR that is comprised by the human antibody. The antibody, in most cases will also have other CDR regions, framework regions as well as optionally constant domains. Therefore the open-ended language correctly reflects the invention, "the antibody comprises a heavy or light chain CDR region...".

In response, other than the specific human monoclonal antibody that binds to human PDGF-D comprising the specific combination of heavy and light chains as set forth in claim 23,

there is insufficient written description about the structure of the light chain in the monoclonal antibody in claim 1 without the amino acid sequence. Further, the specification discloses only human monoclonal antibody or antigen binding portion thereof that specifically binds to human PDGF-D. There is a lack of a written description about the other PDGF-D to which the claimed antibody binds.

With regard to claims 22, 30, 32 and 42, the family genes such as human "VH1-8 family gene", any "JH6B family gene" and/or human "D5-18 family gene" as recited in claims 22, 30, 32, and 42-43 without the nucleotide sequence have no structure, much less function. The specification provides insufficient written description about which particular VH1-8 family gene and JH6B family gene encode the claimed antibody or which undisclosed human monoclonal antibody that binds to all PGDF-D is derived from which particular human V_H1-8 family gene and J_H6B family gene without the nucleotide sequence (claims 22, 32 and 42). Further, the term "gene" as defined by Merriam-Webster's Online Dictionary, 10th Edition is a segment of DNA that is involved in producing a polypeptide chain; it can include regions preceding and following the coding DNA as well as introns between the exons. However, the specification provides insufficient written description about the introns as well as exons in the germ line that encodes the undisclosed human monoclonal antibody, let alone a gene from the human VH1-8 and JH6B gene that encode any human monoclonal antibody or antigen binding portion thereof that specifically binds to all Platelet Derived Factor D (PDGF-D). Since the structure of the claimed antibody mentioned above are not adequately described, it follows that any human monoclonal antibody further comprises a detectable marker are not adequately described. It also follows that any composition comprising any human monoclonal antibody mentioned above are not adequately described.

In response to Applicants' argument the antibody, in most cases will also have other CDR regions, framework regions as well as optionally constant domains. Therefore the open-ended language "comprising" in claims 24-29 and 34-39 correctly reflects the invention, it is correct that antibody contains CDR1-3 from heavy and light chains, framework regions as well as optionally constant domains. However, claim 24 as written lacks the CDR2 and CDR3 from heavy chain, and CDR1, CDR2 and CDR3 from the light chain, for example. Claim 25 as written lacks the CDR1 and CDR3 from the heavy chain, and CDR1-3 from the light chain. Claim 26 as written lacks the CDR1-2 from heavy chain and CDR1-3 from the light chain. Claim 27 as written lacks the CDR1-3 from the heavy chain and CDR2-3 from the light chain. Claim 28 as

written lack the CDR1-3 from the heavy chain, and CDR1 and CDR3 from the light chain. Likewise, claim 29 lacks the CDR1-3 from the heavy chain and CDR1-2 from the light chain. The same reasons apply to claims 34-39. There is inadequate written description about the other undisclosed CDRs mentioned above in said claims without the specified amino acid sequence.

Finally, the specification discloses only human PDGF-D to which the claimed antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of PDGF-D to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 22, 30-32, 40-43 and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,706,687 (March 16, 2004; PTO 892) in view of Green et al (Nature Genetics 7: 13-21, May 4, 1994; PTO 892).

The '687 patent teaches monoclonal antibody and antigen binding portion thereof that binds to platelet derived growth factor D (PDGFD) (See column 10, lines 63-44, in particular).

The reference further teaches the reference antibody is labeled with a detectable marker such as FITC for detection assay (See column 11, lines 10-23, in particular). The reference antibody is useful as inhibitor or agonist of PDGF-D or diagnostic assays (See column 10, line 61-63, in particular).

The claimed invention in claims 22, 32 and 42 differs from the reference only that the monoclonal antibody that specifically binds to Platelet Derived Growth Factor is human monoclonal antibody instead of mouse monoclonal antibody and is encoded by or derived from a human VH1-8 family agene and a JH6B family gene.

The claimed invention in claims 30, 40 and 43 differs from the reference only that the human monoclonal antibody that specifically binds to Platelet Derived Growth Factor further comprises a sequence derived from human D5-18 family gene.

Green et al teach a method of making human antibody that binds to any antigen of interest wherein the reference antibody is encoded by or derived from a one of the human VH1-8 family agene such as VH6 and a JH6B family of gene such as J6 family gene (See Table 2, page 16, clone μ100, in particular). The reference antibody further comprises a sequence encoded by a human D family of gene such as TGGTTATTAC (See Table 2, page 16, clone μ100, in particular). The reference teaches that fully human monoclonal antibody is that the antibody is less immunogenic, and thus more suited for repeated administration (See page 20, column 1, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make human monoclonal antibody as taught by Green et al that binds to PGDF-D as taught by the '687 patent for a fully human monoclonal antibody encoded by human VDJ genes. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Green et al teach that fully human monoclonal antibody is that the antibody is less immunogenic, and thus more suited for repeated administration (See page 20, column 1, last paragraph, in particular). The '687 patent teaches antibody PDGF-D is useful as inhibitor or agonist of PDGF-D or diagnostic assays (See column 10, line 61-63, in particular).

Applicants' arguments filed 11/19/04 have been fully considered but are not found persuasive.

Applicants' position is that Green et al are concerned with engineering a mouse system that can produce the diverse repertoire of human V, D, J combinations that in turn produce the huge diversity of human antibody specificities. Green does not teach which V to combine with which J and/or D gene to provide a certain specificity of antibody. Green does not teach which V, J or D gene will provide an antibody that binds to PDGFD. Applicants respectfully submit that the present invention has identified specific germline human antibody heavy chain V, D, J combinations and light chain V, J combinations including nucleotide and amino acid sequence of the VH and VL domain FR and CDR regions that bind PDGFD from a diverse repertoire. VH1-8 is a specific heavy chain V gene, described on page 62, line 30 to page 63, line 3 of the current specification. JH6B is a specific heavy chain J gene, known in the art and described by Rabbitts, T. H. (1983). Biochem. Soc. Trans., 11, 119-126. D5-18 is a specific heavy chain D region known in the art and described by Corbett et al (1997). J. Mol. Biol., 270, 587-597. Until the applicants' invention was made, it would not have been known to specifically use VH1-8, VH6b and D5-18 to provide for a human antibody that binds to PDGFD.

In response, the nucleotide sequences of "VH1-8", VH6B" and "D5-18" that encode the claimed human antibody that binds to human PDGF-D are not recited in the claims. In the absence of the specific nucleotide sequences of "VH1-8", VH6B" and "D5-18", the process of recombination in the method as taught by Green would produce the claimed invention.

10. Claims 2, 23, 33 and 44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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